European Radiology (2019) 29:4389–4399
https://doi.org/10.1007/s00330-018-5805-4

GASTROINTESTINAL

Non-measurable infiltrative HCC: is post-contrast attenuation on CT a sign of tumor response?

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Received: 7 July 2018 / Revised: 7 September 2018 / Accepted: 25 September 2018 / Published online: 9 November 2018

Abstract

Objectives To evaluate the value of CT attenuation to assess the response to sorafenib in infiltrative/endovascular non-measurable advanced hepatocellular carcinoma (HCC).

Methods From 2007 to 2014, patients with infiltrative HCC ± tumor-in-vein (TIV) were retrospectively included. Attenuation of tumors and TIV were measured at baseline and follow-up on arterial and portal venous phase CT by two independent radiologists. Attenuation changes (overall and as per Choi criteria) and Child-Pugh score were correlated to overall survival.

Results Forty patients were included (38 men, 95%). Attenuation of both the tumors and TIV was significantly lower in follow-up CT than on baseline CT ($p = 0.002$ (arterial), and $p = 0.001$ (portal) for tumor, and $p = 0.004$ (arterial) and $p < 0.001$ (porta) for TIV). Median attenuation of TIV was significantly lower than that of the tumor in follow-up images ($p = 0.010$). Median OS for the entire cohort was 4 ± 1 months (95% CI: 2.1–5.9), with estimated OS rates at 6, 12, and 24 months of 43%, 29 and 12%, respectively. Baseline and follow-up CT attenuation in tumors and TVI were not correlated with survival. Survival was not significantly increased in patients with Choi criteria >15% CT HU decrease in the tumor and/or TIV during follow-up. Only Child-Pugh A (HR 4.9 (95%CI 2.3–10.7), $p < 0.001$) was identified as an independent factor of improved survival on multivariate analysis.

Conclusion Despite significant changes under sorafenib, tumor attenuation of infiltrative/endovascular non-measurable HCC may be of limited value to assess survival in this subgroup of patients with very poor prognosis.

Key Points

- *Attenuation of both tumors and tumor-in-vein decreases after sorafenib.*
- *Attenuation decrease is more marked in the tumor-in-vein than in the tumor.*
- *Attenuation decrease is not associated with longer overall survival.*

Keywords Sorafenib · Carcinoma, hepatocellular · Portal vein · Follow-up studies

Abbreviations

AFP	Alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CT	Computed tomography
EASL	European Association for the Study of the Liver
HCC	Hepatocellular carcinoma
ICC	Intraclass correlation coefficient
(m)RECIST	(modified) Response Criteria In Solid Tumors
ROI	Region of interest
TIV	Tumor-in-vein

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-018-5805-4) contains supplementary material, which is available to authorized users.

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Introduction

According to the Barcelona Clinic Liver Cancer (BCLC) management algorithm [1], patients with advanced-stage hepatocellular carcinoma (HCC), i.e., with malignant venous invasion (further referred to as tumor-in-vein (TIV)), or

extrahepatic disease, as well as those with tumors that do not respond to locoregional treatments, are candidates for first-line treatment with sorafenib (Nexavar®; Bayer Pharma); multikinase inhibitor induces tumor necrosis and devascularization. Indeed, results from a phase II trial [2] and two large multicenter, double-blind, placebo-controlled randomized phase III trials have established sorafenib as a standard of care that prolongs overall survival (OS) in these patients [3, 4].

Imaging criteria used to assess tumor response of HCC are dimension-based and require measuring either the entire targeted tumors (Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) [5, 6]), or their viable part defined as areas showing contrast uptake on imaging (European Association for the Study of the Liver (EASL) criteria [7] or modified RECIST (mRECIST) [8]). The latter have been showed to be better than RECIST criteria in patients receiving sorafenib because they better capture drug-induced devascularization that presents as decreased contrast uptake. Yet in 7 to 20% of the patients [9, 10], HCC is infiltrative, is ill-defined, and cannot be securely identified or separated from the surrounding liver, making the evaluation of tumor response challenging with these criteria. HCC may also be almost exclusively endovascular, once again limiting the use of dimension-based criteria.

To evaluate the response to imatinib, another targeted agent used in gastrointestinal stromal tumors, Choi et al developed composite criteria integrating changes in tumor size and CT tumor attenuation. The latter parameter reflects areas of tumors with reduced vascularization [11, 12]. The Choi criteria accurately predicted the efficacy of imatinib in gastrointestinal stromal tumors and have been shown to be promising in patients with HCC treated with sorafenib [13, 14]. Thus, as infiltrative tumor and/or TIV cannot be measured adequately, CT tumor attenuation could be a viable alternative, and be used as an indicator of the antitumoral effect of sorafenib.

Therefore, this study retrospectively correlated attenuation changes before and after treatment and overall survival in patients with non-measurable HCC.

Material and methods

Patient selection

This retrospective single-center cohort study was approved by the local IRB and informed consent was waived. From 2007 to 2014, all consecutive patients with HCC treated by sorafenib in Beaujon University Hospital were identified. The decision to treat patients with sorafenib was made by a multidisciplinary tumor board according to European Medicines Agency Good Practice Recommendations. Sorafenib was selected when no surgical or locoregional approaches were indicated in patients with good performance status (ECOG 0-1) and adequate liver function (Child-Pugh ≤ B7) (Supplemental material). All patient data were obtained from a prospectively collected clinical and pathological database of HCC patients.

A study coordinator (MR) reviewed all CTs and medical charts. To be eligible, patients had to have non-measurable HCC and had to have received at least four total weeks of sorafenib. Therefore, all patients with measurable disease (i.e., well-delineated disease) were excluded even if TIV was present. Non-measurable HCC was defined as ill-defined tumors with no clear delineation between the tumor and the surrounding liver parenchyma on contrast-enhanced CT at the arterial or portal vein phase. Tumors could be either hypervascular or not, and there was no size limitation.

Patients underwent baseline thoraco-abdominal CT up to 6 weeks before sorafenib and had the first tumor evaluation 1–3 months after sorafenib was begun. Patients with CT that could not be evaluated due to technical reasons or performed outside the predefined interval were excluded. Patients with missing data because of early death or who were lost of follow-up were also excluded.

The final population comprised 40 patients (38 men, 95%), median age 61 years old (38–78) (Fig. 1).

CT scan protocols

CT scans were performed on a multidetector CT (64-detector LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA). After acquisition of the unenhanced images, non-ionic iodinated contrast material (iomeprol, Iomeron 350® (Bracco Imaging) or iobitridol (Xenetix 350®, Guerbet)) was injected through a 20-gauge or larger cannula, typically sited in the antecubital fossa, with a mechanical power injector at a rate of 2 mL/kg, with arterial and portal venous phase image acquisition performed after a delay of 35 and 70 to 80 s.

Imaging analysis

CT was anonymized by the study coordinator who did not participate in the readings (MR) and indicated the location of the tumor on a separate sheet. Before the study, readers evaluated a set of 5 patients that were not included in this study for training. A debriefing session was then held to discuss difficulties and have the same approach when selecting relevant lesions and slice level and when applying criteria.

CT was independently reviewed by two readers (one senior resident, HK, and one consultant abdominal radiologist with 5 years of experience, WA) on a PACS workstation

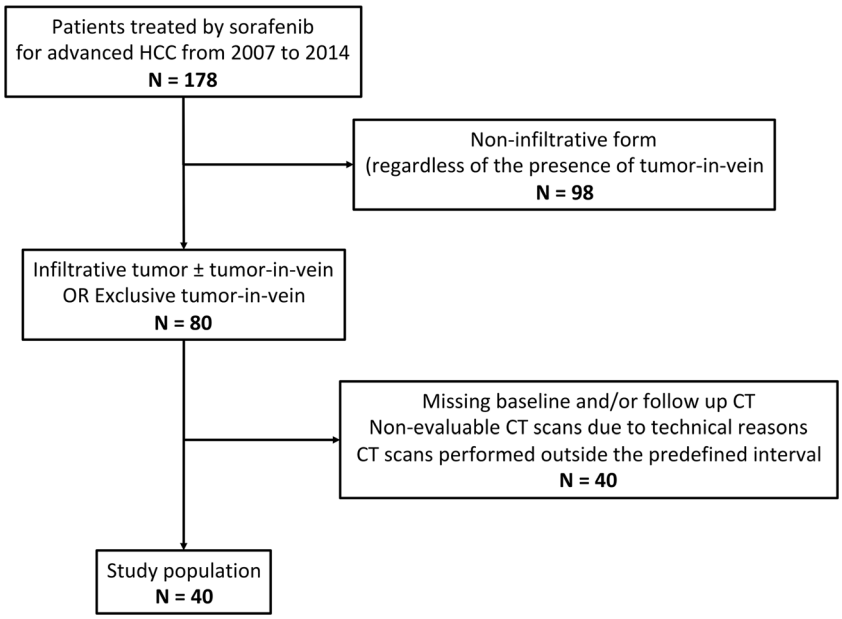

Fig. 1 Flow chart of the study population

(Carestream Health). All CTs were pooled (i.e., baseline and follow-up) and presented randomly to avoid bias and blindly to patients' clinical data and outcome.

Readers were asked to report the following:

- Attenuation of infiltrative HCC and tumor-in-vein, if present, using both a free-hand and circular drawing of a region of interest (ROI), on arterial and portal venous phase images, at both baseline and follow-up. ROI was not copy-pasted but manually reproduced and was as large as possible within the malignant areas. The chosen image was that with the largest image of the tumor, including necrotic areas. The surrounding liver parenchyma was not included in the ROI. ROI positions were validated by the study coordinator.
- Semi-quantitative evaluation of necrosis in infiltrative tumors, defined as a hypoattenuating and non-enhancing area. It was scored as absent, < 25%, 25–50%, and > 50% of the total tumor volume.
- Largest diameter of tumor-in-vein, when present.
- Attenuation of non-tumoral liver using a circular ROI on arterial and portal venous phase images at both baseline and follow-up.

After these readings, readers were asked to compare baseline and follow-up CTs and assess visually:

- Appearance of new intrahepatic or distant HCC
- Increase in size of tumor-in-vein (when present)
- Development of ascites

During this final comparison, no additional quantitative measurement was allowed.

Statistical analysis

Continuous variables were presented as means (standard deviations) or medians (range or interquartile range [IQR]), and categorical variables as frequencies (percentages). Quantitative variables were compared using the Student *t* test or the Mann-Whitney *U* test depending on distribution, assessed using the Kolmogorov-Smirnov test. Qualitative variables were compared using the chi-square or Fisher exact tests.

A 15% change in attenuation was considered to be a significant tumor response according to Choi criteria [12]. OS was measured from the date of treatment onset begun to the date of death, regardless of the cause, or censored at the last follow-up visit. Survival curves were prepared using the Kaplan-Meier method and were compared using the log-rank Mantel-Cox test in accordance with the final responses and with clinical and laboratory tests.

Inter-reader agreement was assessed using the Cohen kappa statistics for categorical data. Inter-reader agreement for continuous variables was evaluated using the intraclass correlation coefficient (ICC), the Bland-Altman plot, and the Spearman correlation test. All statistical tests were two-tailed. A p value < 0.05 was considered to be significant. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (v20.0. SPSS Inc.).

Results

Patient and tumor characteristics

Patient and baseline disease characteristics are presented in Table 1.

Most patients had cirrhosis ($n = 33$, 83%). The majority of patients had excessive alcohol consumption ($n = 14$, 35%), or viral infection (HCV $n = 15$, 38%; HVB $n = 12$, 30%). Twenty-seven patients were Child-Pugh A (67%), and others were Child-Pugh B (23%).

Thirty-seven patients (93%) had both infiltrative tumors and tumor-in-vein. Others had only infiltrative HCCs. HCCs were located in the right or left livers in respectively 13 (33%) and 7 (17%) patients, and the disease was bilobar in 20 patients (50%).

Treatment with sorafenib lasted a median 106 days (34–572). The median time between treatment initiation and the first tumor evaluation was 56 days (13–92). Median follow-up was 6 months (range 1–77).

Tumor CT attenuation measurements

Baseline tumor attenuations are reported in Table 2.

Briefly, on arterial phase images, median baseline attenuation of tumors for readers 1 and 2 was 74 HU (IQR 56–96) and 78 HU (IQR 63–98), respectively, with circular ROIs, and 77 HU (IQR 63–98) and 80 HU (IQR 63–96) with free-hand ROIs. Circular and free-hand CT attenuations were well correlated for both readers ($r = 0.99$, $p < 0.001$ for both readers) with an ICC of 0.99 and 0.99 for readers 1 and 2, respectively.

Attenuation values were significantly correlated between readers for both circular and free-hand ROI ($r = 0.82$, $p < 0.001$ and $r = 0.81$, $p < 0.001$, respectively). Bland and Altman bias and limits of agreements were − 4.1 (IQR – 35, 27) and − 3.3 (IQR − 34, 28) for circular and free-hand ROI measurements, respectively (Table 3).

Similar results were obtained for tumor attenuation on portal venous phase images and for tumor-in-vein on both arterial and portal venous phase images (Table 3).

The baseline attenuation of the tumor and the tumor-in-vein was not significantly different between the readers in the 37 patients with both infiltrative HCC and tumor-in-vein, irrespective of the phase of acquisition (i.e., arterial or portal) or the ROI drawing technique (i.e., free-hand or circular) (Supplemental Table 1). Necrosis was considered absent, < 25%, 25–50%, and > 50% in 26 (65%), 5 (13%), 3 (8%), and 6 (15%) patients, respectively.

Hereafter, and given the low inter-reader and inter-ROI variability, the results of the most experienced reader and of circular ROI measurements are presented.

Changes in tumor and portal vein infiltration attenuation after treatment

The median tumor attenuation on the first follow-up CT was 75 HU (IQR 44–98) and 83 HU (IQR 58–103) on arterial and portal venous phase images, respectively, corresponding to a median decrease of − 9% (IQR − 22, 0) and − 11% (IQR − 19, 0) from baseline. The median attenuation of tumor-in-vein was 69 HU (IQR 49–88) and 70 HU (IQR 53–91) on arterial and portal venous phase images, respectively, corresponding to a median decrease of − 25% (IQR − 27, − 21) and − 14% (IQR − 34, − 6) from baseline (Figs. 2 and 3).

There was a significant decrease in attenuation in both tumor and tumor-in-vein on follow-up arterial and portal venous phase images compared to baseline ($p = 0.002$ and $p = 0.001$ for the tumor, and $p = 0.004$ and $p < 0.001$ for TIV). The median attenuation in patients with tumor-in-vein and infiltrative HCC was significantly lower in the tumor-in-vein than in the tumor ($p = 0.010$; Supplemental Table 1).

Based on Choi 15% attenuation decrease, 18 patients (45%) and 9 patients (23%) had an objective response in the tumors on arterial and portal venous phase images, respectively, and

Table 1 Patient and tumor baseline characteristics ($N = 40$)

Age (years)	
Median	60
Range	38–78
Gender (%)	
Male	38 (95)
Female	2 (5)
Etiology, number of patients (%)	
Viral*	24 (60)
Alcohol	14 (35)
NASH	12 (30)
Child-Pugh score, number of patients (%)	
A	27 (67)
B	13 (33)
BCLC stage, number of patients (%)	
B	2 (5)
C	38 (95)
Laboratory tests (median and IQR)	
Alpha-fetoprotein (UI/L)	108 (16–2083)
Bilirubin (mmol/L)	21 (14–29)
Platelet count (10^9/mL)	173 (100–225)
Prothrombin time %	85 (74–93)
Extrahepatic spread, number of patients (%)	12 (30)
Tumor-in-vein (%)	37 (93)
Prior treatments, number of patients (%)	
None	23 (58)
Surgery	3 (8)
Radiofrequency ablation	3 (8)
Trans-arterial chemoembolization	15 (38)
Median duration of sorafenib in days (range)	106 (34–572)
Median time between initiation and first evaluation, in days (range)	56 (13–92)

BCLC Barcelona Clinic Liver Cancer, *NASH* nonalcoholic steatohepatitis, *IQR* interquartile range

*Patients had HBV and/or HCV infection

Table 2 Tumor CT attenuation measurements and variations of tumors, tumor-in-vein, and liver parenchyma for both readers

	Reader 1				Reader 2			
	Baseline	Follow-up	Variation (%)	*p* value	Baseline	Follow-up	Variation (%)	*p* value
Tumor attenuation (HU)								
Arterial phase								
Free-hand	77 (63–98)	74 (55–98)	− 11 (− 23, − 4)	0.053	80 (63–96)	73 (50–97)	− 11 (− 20, 0)	0.002
Circular	74 (56–96)	73 (60–97)	− 12 (− 18, − 3)	0.058	78 (63–98)	75 (44–98)	− 9 (− 22, 0)	0.002
Portal phase								
Free-hand	90 (72–108)	88 (71–107)	− 8 (− 15, − 1)	0.026	91 (79–105)	84 (66–104)	− 5 (− 14, 0)	0.003
Circular	91 (72–108)	83 (71–104)	− 12 (− 17, − 1)	0.026	90 (80–107)	83 (58–103)	− 11 (− 19, 0)	0.001
Tumor-in-vein attenuation (HU)								
Arterial phase								
Free-hand	79 (69–93)	67 (46–95)	− 27 (− 40, − 8)	0.009	81 (72–93)	69 (52–92)	− 20 (− 37, − 9)	0.004
Circular	79 (66–95)	66 (41–84)	− 16 (− 34, − 2)	0.001	82 (72–97)	69 (49–88)	− 25 (− 27, − 21)	0.004
Portal phase								
Free-hand	85 (77–93)	74 (50–91.5)	− 12 (− 35, − 1)	0.001	89 (76–96)	73 (56–95)	− 17 (− 35, − 9)	< 0.001
Circular	81 (73–95)	68 (49–91.5)	− 11 (− 36, − 3)	0.001	88 (76–99)	70 (53–91)	− 14 (− 34, − 6)	< 0.001
Largest diameter (mm)	19 (15–24)	19 (13–24)	–	0.660	19 (13–23)	18 (11–22)	–	0.521
Liver attenuation (HU)								
Arterial phase	77 (66–87)	81 (70–93)	+ 4 (− 7, + 23)	0.097	76 (64–85)	79 (70–90)	+ 3 (− 6, + 19)	0.135
Portal phase	110 (104–121)	117 (110–129)	+ 4 (− 3, + 17)	0.104	107 (101–121)	118 (109–127)	+ 8 (− 3, + 17)	0.030

Values are expressed as median and interquartile range (25e–75e), *p* values with Mann-Whitney *U* test. ROI sizes were not significantly different when comparing free-hand and circular ROI for both readers and both acquisition times (i.e., arterial phase and portal venous phase). Results are not provided

HU Hounsfield units

21 (53%) and 21 (53%) had an objective response in the area of tumor-in-vein.

Survival analysis

The median OS of the entire cohort was 4 ± 1 months (95% CI 2.1–5.9), with estimated OS rates at 6, 12, and 24 months of 43%, 29%, and 12%, respectively.

On univariate analysis, longer survival was associated with a baseline Child-Pugh A score (median OS 11 ± 4 (3–19) months, $p < 0.001$), absence of tumor necrosis at baseline (median OS 11 ± 3.3 (4.3–18) months, $p = 0.007$), absence of new HCC on follow-up (median OS 13 ± 5 (6.1–19) months, $p < 0.001$), and AFP serum level (i.e., normal at baseline or > 30% decreased after treatment when initially elevated) (median OS 13 ± 3 (7.6–18) months, $p = 0.003$). Other factors were not associated with OS (Table 4).

Baseline and follow-up tumor and TIV CT attenuation were not correlated with survival (Table 5, Figs. 2 and 3). Survival was not longer in patients with a > 15% decrease in mean tumor attenuation on follow-up CT regardless of the phase of acquisition. Similar results were observed with TIV attenuation alone, or TIV in combination with tumor attenuation (Table 4).

Multiple regression analysis only showed Child-Pugh A (HR 4.9 (95% CI 2.3–10.7), $p < 0.001$) to be associated with improved survival (Table 4).

Discussion

This study showed that attenuation of both tumors and tumor-in-vein significantly decreased after sorafenib treatment on the first follow-up CT. This decrease was significantly more marked for the tumor-in-vein. Nevertheless, these variations were not associated with modifications of overall survival. The only independent factor of prolonged survival in these patients was baseline liver function.

The added value of tumor attenuation on CT for the assessment of tumor response to treatment appeared limited. Indeed, although the effect of sorafenib could be demonstrated by a significant decrease in the attenuation of both tumor and tumor-in-vein as shown by previous studies [15, 16], these changes did not influence overall survival in the current study. These results are not in line with previous studies reporting a longer survival in patients considers as responders according to modified Choi's criteria [13, 14]. This discrepancy is probably due to the difference in study populations between the present study and previous ones. Indeed, their conclusions

Table 3 Intra- and inter-reader agreement for tumor and tumor-in-vein (TIV) attenuation measurements

	Baseline					Follow-up				
	Correlation			Bland and Altman		Correlation			Bland and Altman	
	r	*p*	ICC	Bias	95% LOA	*r*	*p*	ICC	Bias	95% LOA
Intra-observer										
Tumor attenuation (free-hand vs. circular)										
Arterial phase										
Reader 1	0.99	< 0.001	0.99	1.3	− 5.2, 7.7	0.99	< 0.001	0.99	1.0	− 6.4, 8.4
Reader 2	0.99	< 0.001	0.99	0.7	− 5.2, 6.6	0.99	< 0.001	0.99	0.9	− 6.9, 8.7
Portal phase										
Reader 1	0.99	< 0.001	0.99	− 0.7	− 7.5, 6.1	0.96	< 0.001	0.98	1.3	− 12, 15
Reader 2	0.99	< 0.001	0.99	1.2	− 5.0, 7.4	0.94	< 0.001	0.99	2.7	− 5, 10
TIV attenuation (free-hand vs. circular)										
Arterial phase										
Reader 1	0.94	< 0.001	0.96	0.8	− 18, 19	0.92	< 0.001	0.97	2.5	− 18, 23
Reader 2	0.93	< 0.001	0.95	1.1	− 14, 17	0.94	< 0.001	0.98	1.7	− 14, 17
Portal phase										
Reader 1	0.93	< 0.001	0.97	2.4	− 14, 19	0.84	< 0.001	0.98	3.1	− 13, 19
Reader 2	0.97	< 0.001	0.98	2.5	− 6.6, 11	0.77	< 0.001	0.98	2.8	− 10, 16
Inter-observer										
Tumor attenuation (reader 1 vs. 2)										
Arterial phase										
Free-hand	0.82	< 0.001	0.88	− 3.3	− 34, 28	0.92	< 0.001	0.96	0.8	− 19, 21
Circular	0.83	< 0.001	0.90	− 4.1	− 35, 27	0.86	< 0.001	0.94	0.5	− 22, 24
Portal phase										
Free-hand	0.78	< 0.001	0.76	− 4.5	− 41, 32	0.83	< 0.001	0.91	− 0.2	− 29, 29
Circular	0.75	< 0.001	0.84	− 2.7	− 39, 34	0.78	< 0.001	0.87	1.5	− 33, 37
TIV attenuation (reader 1 vs. 2)										
Arterial phase										
Free-hand	0.83	< 0.001	0.91	− 3.9	− 30, 22	0.82	< 0.001	0.91	− 2.2	− 35, 30
Circular	0.84	< 0.001	0.92	− 3.7	− 31, 24	0.87	< 0.001	0.92	− 2.2	− 34, 29
Portal phase										
Free-hand	0.91	< 0.001	0.95	− 4.1	− 22, 14	0.92	< 0.001	0.96	− 2.9	− 23, 17
Circular	0.87	< 0.001	0.93	− 4.1	− 24, 16	0.89	< 0.001	0.94	− 1.9	− 28, 24

Correlation with the Spearman test

ICC intraclass correlation coefficient, *TIV* tumor-in-vein, *LOA* limits of agreement

were drawn from an analysis of patients with advanced HCC including, but not limited to, infiltrative forms with tumor-in-vein. Our study population evaluated the latter subgroup. The prognosis of this subgroup is poor with a median OS ranging from 1.9 [10] to 10 months [17]. This probably explains why the median OS in our patients was only 4 months, while it was 10.5 months and 12.8 months in the studies by Gavanier et al and Ronot et al, respectively [13, 14], closer to that reported in the seminal SHARP trial [3]. Another possible explanation is that tumor attenuation may be an inadequate imaging criterion for infiltrative tumors. Indeed, infiltrative tumors are usually less hypervascular than non-infiltrative HCCs; thus, changes in tumor attenuation during treatment may be limited. This would require further investigation.

One might consider that based on the abovementioned findings, follow-up CT is of limited use and could be avoided as in routine practice, the decision to maintain or stop sorafenib being primarily based on continuous reassessment of safety and efficacy. Yet, CT remains very important to detect tumor progression, especially occurrence of new lesions that was associated with a poorer prognosis in the present study. Noticeably, all recently introduced imaging criteria have focused on the identification of responders and have not significantly modified criteria for tumor progression that is still performed according

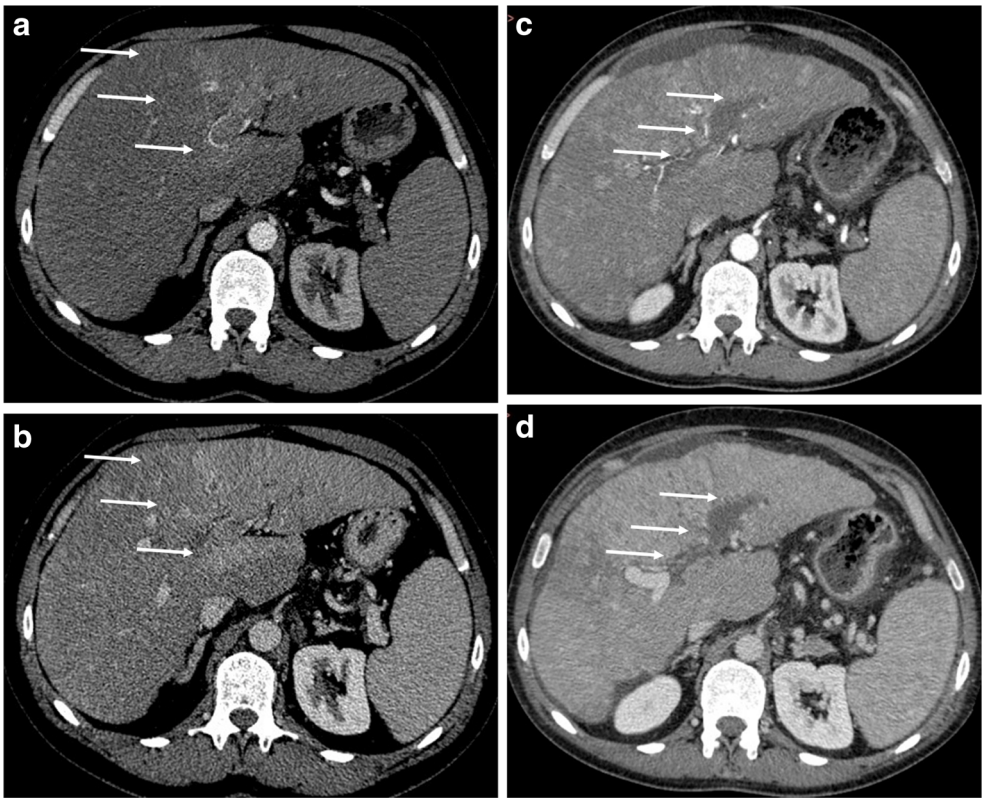

Fig. 2 Infiltrative HCC with left tumor-in-vein in a 41-year-old male with alcohol and HCV-related Child A cirrhosis. He had no extrahepatic disease. Baseline contrast-enhanced CT on arterial (**a**) and portal venous phase (**b**) showed heterogeneous infiltration of the left liver with tumor-in-vein showing arterial phase hyperenhancement and washout (arrows). On first CT follow-up, the liver appeared more heterogeneous, and the tumor-in-vein presented signs of devascularization on both arterial (**c**) and portal venous phase (**d**) (arrows) as shown by a 41% and 50% median attenuation decrease, respectively. The patient survived 6 months after the introduction of sorafenib

to the RECIST criteria, with the exception of tumor viability. Therefore, and paradoxically, it may be that the simple RECIST criteria remain useful in this subgroup of patients with infiltrative HCC in the era of sophisticated imaging criteria.

In patients with tumor-in-vein, the CT attenuation variation of the latter was higher than that of the infiltrative tumor on CT follow-up, especially on portal venous phase images somehow suggesting a more marked devascularization of the

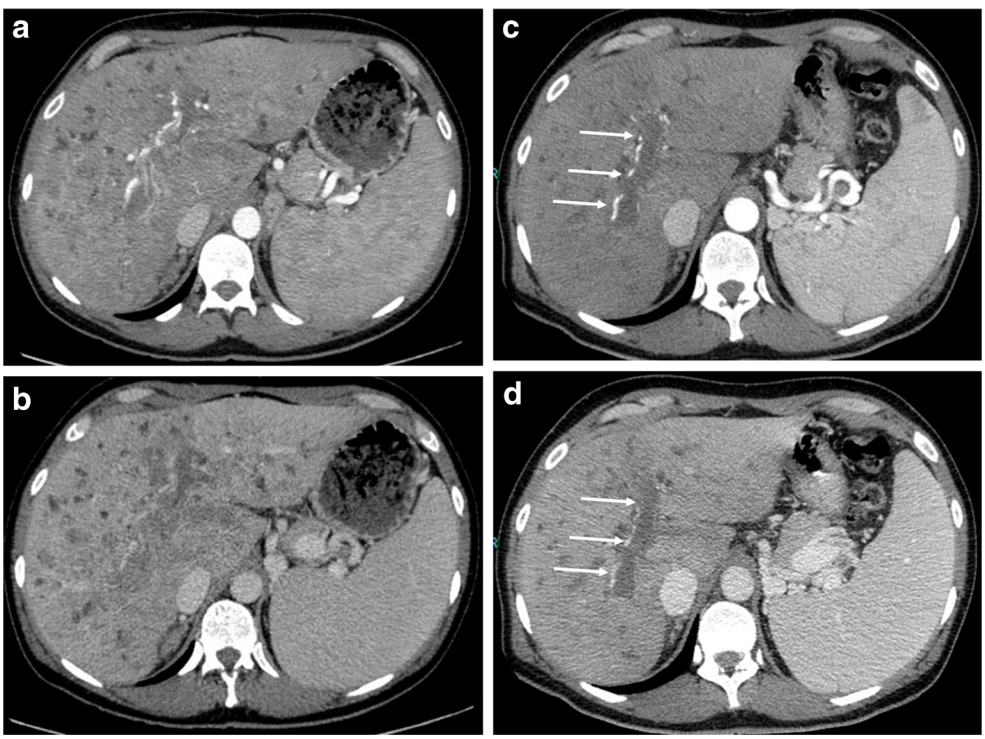

Fig. 3 Bilobar infiltrative HCC with tumor-in-vein in a 50-year-old male with HCV-related Child A cirrhosis. He had no extrahepatic disease. Baseline contrast-enhanced CT on arterial (**a**) and portal venous phase (**b**) showed heterogeneous infiltration of the liver with tumor-in-vein showing arterial phase hyperenhancement and washout. On first CT follow-up, the liver appeared more heterogeneous, and the tumor-in-vein presented signs of devascularization on both arterial (**c**) and portal venous phase (**d**) (arrows). The tumor-in-vein showed a 48% and 57% median attenuation decrease, on arterial and portal venous phase images, respectively. The patient survived 3 months after the introduction of sorafenib

Table 4 Factors associated with overall survival

		OS (median months, 95% CI)	*p* value Log-rank	HR (95% CI)	*p* value Cox model
Overall		4 ± 1 (2.1–5.9)			
Patients					
Gender	Male	4 ± 1 (2.1–5.9)	0.065		0.151
	Female	-[a]			
Cirrhosis	Yes	6 ± 2 (2.4–9.6)	0.194		
	No	4 ± 1 (1.7–6.3)			
Extrahepatic disease	Yes	4 ± 0.4 (3.2–4.7)	0.272		
	No	6 ± 3 (0.2–11.8)			
Tumor-in-vein	Yes	4 ± 2 (0.8–7.2)	0.431		
	No	6 ± 1 (4.0–7.9–11.8)			
BCLC	B	6 ± 1 (4–8)	0.431		
	C	4 ± 1.6 (0.8–7.2)			
Child-Pugh	A	11 ± 4 (3–19)	< 0.001	4.9 (2.3–10.7)	< 0.001
	B	3 ± 0.6 (1.8–4.1)			
Alpha-fetoprotein (UI/L)					
Baseline	> 100	4 ± 1.5 (1–7)	0.476		
	> 1000	4 ± 0.7 (2.5–5.5)	0.351		
Variation	N at baseline or decrease > 30%	13 ± 3 (7.6–18)	0.003		0.345
Bilirubin at baseline (mmol/L)	0–2N	6 ± 2 (2–10)	0.313		
	> 2N	4 ± 1.2 (1.7–6.3)			
Necrosis on baseline CT	Yes	4 ± 0.3 (3.5–4.5)	0.007		0.835
	No	11 ± 3.3 (4.3–18)			
CT attenuation variation*					
Tumor arterial phase	< 15%	6 ± 2.2 (1.7–10)	0.926		
	≥ 15%	4 ± 1.2 (1.6–6.4)			
Tumor portal phase	< 15%	6 ± 2.1 (1.8–10)	0.162		
	≥ 15%	4 ± 0.7 (2.6–5.4)			
TIV arterial phase	< 15%	4 ± 1.1 (1.1–6.9)	0.894		
	≥ 15%	4 ± 1.5 (1.9–6.1)			
TIV portal phase	< 15%	6 ± 3.9 (0–13)	0.653		
	≥ 15%	4 ± 0.5 (3.1–4.9)			
Tumor OR TIV arterial phase	< 15%	4 ± 1.4 (1.3–6.8)	0.251		
	≥ 15%	4 ± 1.2 (1.6–6.4)			
Tumor OR TIV portal phase	< 15%	4 ± 0.5 (3.1–4.8)	0.110		
	≥ 15%	11 ± 4.5 (2.1–20)			
Follow-up CT					
New lesion	Yes	4 ± 0.3 (3.5–4.5)	< 0.001		0.121
	No	13 ± 3.5 (6.1–19)			
TIV extension	Yes	3 ± 1.8 (0.6–5.4)	0.110		
	No	6 ± 1.9 (2.3–9.7)			
Apparition of ascites	Yes	4 ± 0.5 (3.1–4.9)	0.067		0.310
	No	11 ± 4.4 (2.2–20)			

BCLC Barcelona Clinic Liver Cancer, *HR* hazard ratio, *OS* overall survival, *95% CI* 95% confidence interval, *TIV* tumor-in-vein, *N* normal value

*Results are provided for the most experienced reader (reader 2) with free-hand ROI

[a] Only two patients

Table 5 Correlation between tumor CT attenuation measurements and attenuation variation and overall survival (OS) (Spearman *r* correlations)

	Reader 1				Reader 2			
	Tumor		Tumor-in-vein		Tumor		Tumor-in-vein	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Arterial phase								
Baseline								
Free-hand	0.273	0.152	0.267	0.115	0.145	0.422	0.108	0.532
Circular	0.289	0.129	0.308	0.068	0.188	0.296	0.103	0.550
Follow-up								
Free-hand	0.197	0.335	− 0.012	0.965	− 0.023	0.903	− 0.042	0.982
Circular	0.184	0.367	0.031	0.871	− 0.042	0.809	− 0.071	0.701
Variation								
Free-hand	0.154	0.462	− 0.154	0.401	− 0.026	0.877	− 0.026	0.885
Circular	0.139	0.508	− 0.151	0.389	− 0.089	0.597	− 0.060	0.734
Portal phase								
Baseline								
Free-hand	0.308	0.104	0.323	0.068	− 0.034	0.892	0.231	0.175
Circular	0.331	0.079	0.323	0.055	0.091	0.600	0.202	0.237
Follow-up								
Free-hand	0.270	0.173	0.053	0.754	− 0.034	0.866	0.063	0.720
Circular	0.369	0.058	0.081	0.656	− 0.032	0.884	0.072	0.690
Variation								
Free-hand	0.073	0.703	− 0.208	0.224	0.152	03550	− 0.110	0.531
Circular	0.138	0.501	− 0.196	0.253	0.017	0.918	− 0.103	0.556

endovascular component. Unfortunately, this imaging finding did not translate into a better identification of long survivors. As a consequence, our results show that the devascularization of the tumor-in-vein is more a stigmata of the treatment by sorafenib, than a marker of response per se.

In the study of Ronot et al, the inter-observer agreement observed with weighted kappa values was moderate for the Choi criteria ($k = 0.58$) [13]. We have evaluated both intra- and inter-reader agreement of the CT attenuation of the tumor and tumor-in-vein and showed that they were good to excellent for both the tumor and the tumor-in-vein. We have analyzed the influence of the acquisition phase by comparing arterial and portal phase images. It is an important issue because the initial Choi criteria for GIST were described on the portal venous phase [12] and were applied to the arterial phase in HCC studies [13, 14]. We have shown no difference between the two sets of measurements. We have also analyzed the influence of the CT attenuation measurement by comparing manually drawn and circular ROI methods. Our results showed that the free-hand method was not superior to the circular ROI one, in line with other studies [13]. Overall, it seems that circular ROIs are accurate and reproducible enough. Moreover, circular ROIs are easier and quicker to apply in routine practice.

Several recent studies have shown that 3D evaluation might be superior to 2D criteria for the assessment of HCC response to locoregional treatment [18–22]. Similar approaches are needed in patients treated with sorafenib and may help overcome the limitation of 2D measurement. Recent technical developments may also help improve tumor response assessment in patients with HCC by better capturing the antitumoral effect of treatments at a microvascular level. Recent studies have suggested that perfusion changes might be helpful to monitor the anti-tumor activity [23, 24]. Mulé et al demonstrated that iodine concentration derived from dual-energy CT late-arterial phase was significantly related to perfusion parameters and could be used to assess perfusion changes [25]. More recently, Lee et al showed in an animal model that photoacoustic imaging could measure tumor oxygen saturation changes induced by sorafenib, thus helping monitoring the therapeutic response of HCC [26]. Whether or not these promising results can be translated into patients with infiltrative forms of HCC remains to be demonstrated in further studies.

Aside from its retrospective design, our study suffers from several limitations. First, the total number of patient was limited. Nevertheless, the population was fairly large one when considering such a rare pattern of HCC treated with sorafenib.

One larger descriptive study comparing nodular and infiltrative forms of HCC found only 135 patients with an infiltrative form over a period of 6 years among 224 patients with advanced HCC [10]. Second, we did not evaluate patients with MR imaging. Yet, tumor attenuation measurements have only been described with CT. Third, cause of death was not univocal in all patients since tumor progression might prompt signs of liver failure and/or portal hypertension. Finally, we did not adjust for eventual differences in cardiovascular output. This may have biased the attenuation measurement. Yet, given the short time delay between baseline and follow-up CT, we believe that the calculation of attenuation differences for a given patient was only marginally affected.

To conclude, tumor and tumor-in-vein CT attenuation significantly change under sorafenib reflecting the antitumoral effect of treatment in patients with infiltrative HCC. Yet, these changes may not be helpful to predict survival in this subgroup of patient with very poor prognosis.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Maxime Ronot.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Ethical approval Institutional Review Board approval was obtained.

Informed consent Written informed consent was waived by the Institutional Review Board.

Methodology
- retrospective
- diagnostic or prognostic study
- single-center study

References

1. Forner A, Reig ME, de Lope CR et al (2010) Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30:61–74
2. Abou-Alfa GK, Schwartz L, Ricci S et al (2006) Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 24:4293–4300
3. Llovet JM, Ricci S, Mazzaferro V et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390
4. Cheng AL, Kang YK, Chen Z et al (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25–34
5. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
6. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
7. Bruix J, Sherman M, Llovet JM et al (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 35:421–430
8. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30:52–60
9. Reynolds AR, Furlan A, Fetzer DT et al (2015) Infiltrative hepatocellular carcinoma: what radiologists need to know. RadioGraphics 35:371–386
10. Yopp AC, Mokdad A, Zhu H et al (2015) Infiltrative hepatocellular carcinoma: natural history and comparison with multifocal, nodular hepatocellular carcinoma. Ann Surg Oncol 22(Suppl 3):S1075–S1082
11. Choi H, Charnsangavej C, Faria SC et al (2007) Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 25:1753–1759
12. Choi H, Charnsangavej C, de Castro Faria S et al (2004) CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol 183:1619–1628
13. Ronot M, Bouattour M, Wassermann J et al (2014) Alternative Response Criteria (Choi, European association for the study of the liver, and modified Response Evaluation Criteria in Solid Tumors [RECIST]) Versus RECIST 1.1 in patients with advanced hepatocellular carcinoma treated with sorafenib. Oncologist 19:394–402
14. Gavanier M, Ayav A, Sellal C et al (2016) CT imaging findings in patients with advanced hepatocellular carcinoma treated with sorafenib: alternative response criteria (Choi, European Association for the Study of the Liver, and modified Response Evaluation Criteria in Solid Tumor (mRECIST)) versus RECIST 1.1. Eur J Radiol 85:103–112
15. Salvaggio G, Furlan A, Agnello F et al (2014) Hepatocellular carcinoma enhancement on contrast-enhanced CT and MR imaging: response assessment after treatment with sorafenib: preliminary results. Radiol Med 119:215–221
16. Kim MJ, Choi JI, Lee JS, Park JW (2011) Computed tomography findings of sorafenib-treated hepatic tumors in patients with advanced hepatocellular carcinoma. J Gastroenterol Hepatol 26:1201–1206
17. Kneuertz PJ, Demirjian A, Firoozmand A et al (2012) Diffuse infiltrative hepatocellular carcinoma: assessment of presentation, treatment, and outcomes. Ann Surg Oncol 19:2897–2907
18. Chapiro J, Duran R, Lin M et al (2015) Early survival prediction after intra-arterial therapies: a 3D quantitative MRI assessment of tumour response after TACE or radioembolization of colorectal cancer metastases to the liver. Eur Radiol 25:1993–2003
19. Chapiro J, Lin M, Duran R, Schernthaner RE, Geschwind JF (2015) Assessing tumor response after loco-regional liver cancer therapies: the role of 3D MRI. Expert Rev Anticancer Ther 15:199–205
20. Chapiro J, Wood LD, Lin M et al (2014) Radiologic-pathologic analysis of contrast-enhanced and diffusion-weighted MR imaging in patients with HCC after TACE: diagnostic accuracy of 3D quantitative image analysis. Radiology 273:746–758
21. Tacher V, Lin M, Duran R et al (2016) Comparison of existing response criteria in patients with hepatocellular carcinoma treated

with transarterial chemoembolization using a 3D quantitative approach. Radiology 278:275–284
22. Zhao Y, Duran R, Bai W et al (2018) Which criteria applied in multi-phasic ct can predict early tumor response in patients with hepatocellular carcinoma treated using conventional TACE: RECIST, mRECIST, EASL or qEASL? Cardiovasc Intervent Radiol 41:433–442
23. Ippolito D, Querques G, Okolicsanyi S, Franzesi CT, Strazzabosco M, Sironi S (2017) Diagnostic value of dynamic contrast-enhanced CT with perfusion imaging in the quantitative assessment of tumor response to sorafenib in patients with advanced hepatocellular carcinoma: a feasibility study. Eur J Radiol 90:34–41
24. Kaufmann S, Thaiss WM, Schulze M et al (2018) Prognostic value of perfusion CT in hepatocellular carcinoma treatment with sorafenib: comparison with mRECIST in longitudinal follow-up. Acta Radiol 59:765–772
25. Mule S, Pigneur F, Quelever R et al (2017) Can dual-energy CT replace perfusion CT for the functional evaluation of advanced hepatocellular carcinoma? Eur Radiol. https://doi.org/10.1007/s00330-017-5151-y
26. Lee S, Kim JH, Lee JH, Lee JH, Han JK (2018) Non-invasive monitoring of the therapeutic response in sorafenib-treated hepatocellular carcinoma based on photoacoustic imaging. Eur Radiol 28:372–381